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IRON DEFICIENCY ANAEMIA : EFFECT ON CONGNITIVE DEVELOPMENT IN CHILDREN : A REVIEW

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ABSTRACT

Iron deficiency evolves slowly through several stages. Early iron deficiency caused a depletion in iron stores as shown by a reduction in the levels of hepatic non-heme iron in the new born of iron deficient mothers. Of particular importance is the effect on central nervous system, which leads to the defects in the cognition and learning processes in humans. Evidence is strong that in many under developed countries iron deficiency is the main cause of anaemia and supplementation under trial conditions may prevent some defects of iron deficiency but not all.

KEY WORDS

Anaemia, Iron deficiency, Non-heme iron.

INTRODUCTION

Micronutrient deficiencies are still a major public health problem in the world today with an estimated 2.5 - 5 billion people so affected and specially in developing countries with infants and pregnant women especially at risk (1). In the milder form anaemia is silent without symptoms , while in the severe cases it is associated with fatigue, weakness, dizziness and drowsiness. Infants wants extra concern as iron is actively transferred from mother to fetus during pregnancy, the maximal time of transfer being during the third trimester. As a consequence the premature infant is born with relatively lower iron stores depending on the gestational age. Medical evidence show that very severe anaemia is a direct cause of maternal and child mortality (2). Iron deficiency causes varying degrees of impairment in congnitive performance (3), lowered work capacity, lower immunity to infections (4), pregnancy complication e.g. low birth weight babies, poor learning capacity and reduced phychomotor skills (5). Among the various biological effects of iron, there is considerable evidence that iron is also important for neurological functioning and development. The biological basis of the behavioural and congnitive developmental delays observed in iron deficient infants is not completely understood, but possibly include (i) abnormalities in neurotransmitters metabolism , (ii) decreased myelin formation (iii) alteration in brain energy metabolism (6).

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In this context the nutritional relationship between lactating mothers and their infants is of special interest. Of importance is that the uptake of iron in brain is at its peak during periods of fast neuronal growth (7, 8). Evidence is strong that in many under developed countries iron deficiency is main cause of anaemia. Its effect ranges from simple depletion of iron stores to severe iron deficiency and supplementation under trial conditions, may prevent some defects of iron deficiency anaemia ,but not all (9, 10).

Diagnosis of iron deficiency

The diagnosis of iron deficiency anaemia depends upon the clinical examination with subsequent laboratory confirmation by peripheral blood findings and serum iron studies. Red cell indices will reflect the amount of hemoglobin in the red cells and will vary with severity and duration of anaemia. In the initial stages of iron deficiency red cells may display normal indices with hemoglobin levels of 9 to 12 g/dl, and iron deficient patient with hemoglobin levels below 9 g/dl will display a low MCV (55 - 74 fl) and a low MCH (25 -30 g/dl) and an increased RDW (>16). Examination of the morphology of peripheral blood smears is by itself not fully reliable because (1) with mild degrees of anaemia the blood cells are often normochromic and normocytic and both the blood smear and red cell indices may be with in normal limits (11,12) and (2) when present hypochromia and microcystosis may be due to other causes including the anaemia of chronic diseases, sideroblastic anaemia and thalassemia (13), therefore evidence that body stores are depleted is necessary for secure diagnosis. The most reliable procedure for this purpose is the histochemical estimation of reticuloendothelial iron stores in the aspirated bone marrow particles or biopsy specimens.

The radioimmunometric measurement of serum levels of the iron storage protein, ferritin, has been generally found to correlate well with body iron stores (14). But still these tests are not popular due to lack of sophisticated facilities and training involved.

A more widely used indirect method, involving less cost and patients discomfort is the measure of serum iron and iron binding capacity. However, the direct visual estimation of bone marrow iron stores is necessary for firm diagnosis, in minor cases with hypoalbuminemia or an associated inflammatory disorder along with iron deficiency anaemia.

Clinical Presentation

Iron deficiency in adults usually stems from blood loss in one form or another (whether menstruation, child birth or gastrointestinal pathology) but the most common cause in children is dietary. Major factors in children are (i) introduction of cow's milk (ii) exclusive breast feeding beyond six months (iii) the milkaholics (15).

Iron deficiency progresses in different stages which include depletion of tissue iron that causes a negative iron balance showing a change in a number of laboratory parameters (Table 1). If depletion of iron stores continues anaemia predictably worsens, showing tissue changes as a result of gradually decreasing intracellular levels of iron (15), iron dependent enzymes, caused by prolonged iron depletion.

However, a further difference between children and adults is in the presentation of iron deficiency. What both age groups have in common is that most often the condition will be entirely asymptomatic. Apart from this children may well present with failure to thrive, recurrent infections or minor bahavioural disturbance that are all too easy to dismiss as minor problems of toddlerhood (7, 17).

Studies on developmental scores

The number of studies conducted on older children and adolescents are small in number with poor methodological design. It is not yet clear whether there are large statistically and clinically significant differences in intellectual performance between anaemic and non-anaemic children and adolescents (8).

The most sinister potential problem with iron deficiency is retarded phychomotor and congnitive development and lowered work capacity. Although this may be subtle in an individual child and therefore not really a presenting symptom as such, there is increasing evidence that marked iron deficiency can cause significant CNS damages even in the absence of anaemia (13). There seems to be a vulnerable period

Table 1. Common laboratory tests for the diagnosis of iron deficiency anaemia in young children

S No.	Test	Age (years)	Cut of value
1.	Serum iron	1 -2	< 30 µg/dl (5.4 µmol/l)
		3 -5	< 30 µg/dl
2.	TIBC	1 -3	>480 µg/dl (86 µmol/l)
		3 -5	>470 µg/dl (84 µmol/l)
3.	Haematocrit	1 -2	< 33%
		3 -5	< 34%
4.	MCV	1 -2	< 70 fl (famtolitre)
		3 -5	< 73 fl
5.	MCHC	1 -2	< 32 g/dl
		3 -5	<32 g/dl
6.	RDW	1 -5	>14.5%
7.	Serum Ferritin	1-5	<12 µg/l

TIBC - Total Iron Binding Capacity, MCV - Mean Corpuscular Volume, MCHC - Mean Corpuscular Hemoglobin Concentration, RDW - Red Cell Distribution Width.

for this damages particularly between 9 and 18 months. An even more important issue is that some research has suggested that this damage may not always be reversible when iron stores are corrected even in early stage of iron deficiency. Many of these symptoms are rapidly reversed on iron therapy while others may not. Of particulars importance is the effect on central nervous system which leads to defect in congnition and learning processes in humans (11). Brain is quite sensitive to dietary iron depletion and uses a host of mechanisms to regulate iron flux hemostatically. Within brain there is a system for acquistion of iron from plasma pool transferrin receptors, a mechanism for dispersal and mobilization of iron. The blood - brain barrier is an effective regulatory point for iron from plasma pool to brain. The concentration of iron is maximum at birth, decreases through weaning and then begins to increase with onset of myleination (18) Iron is required for proper myelination of spinal cord and white matter of cerebeller folds in brain and is cofactor for a number of enzymes involved in neurotransmitter synthesis (30). Iron deficiency is associated with alterations in many metabolic processes that may involve brain functioning, among them are neurotransmitter

metabolisms, protein synthesis, organogenesis and others . It has been proposed that alteration in dopamine, 5 Hydroxytryptamine (Serotonin) receptors that follow iron deficiency mediate through neurodevelopmental changes. Early deficiency is also known to affect the levels of gamma amino butyric acid (GABA). Studies in animal models have also shown marked reduction in levels of GABA in brain. Enzymes for biosynthesis of GABA and Glutamate are also reduced. These alterations are irreversible because the defect persists even after supplementation (16, 17).

Correlational studies have found associations between iron deficiency anaemia and poor congnitive and motor development and behavioural problems.

Longitudinal studies alterations consistently indicate that children anemic in infancy have poor congnition, school achievement and more behavioural problems into childhood. There is involvement of iron in synthesis and packaging of neurotransmitters, their uptake and degradation into other iron containing proteins which may directly or indirectly alter the brain function. It is likely due to the failure to deliver iron to brain during particular period of early brain development (12). This could be related to delayed motor malnutrition and perhaps to behaviour in young humans. GABA is an amino acid that acts as a neurotransmitter. There's a high concentration of GABA in the hypothalamus region of the brain, which suggests that it plays a significant role in hypothalamic - pituitary function (19). This means that it assists in hormonal production throughout the body and can positively effects the level of growth hormone.

Common laboratory parameters studied for the diagnosis of iron deficiency anaemia are :

(a) Serum Ferritin (SF)

Serum ferritin is a reliable and sensitive parameter for the assessment of iron stores in healthy subjects. Quantitative phlebotomy has shown a close relationship between serum ferritin concentration and mobilizable iron stores and demonstrated that 1 µg/l of serum ferritin corresponds to 8 -10 mg of storage iron. Serum ferritin is widely used in clinical practice and population screening (20).

Serum ferritin levels below 12 µg/l are highly specific for iron deficiency and denote complete exhaustion of iron stores in adults. A ferritin concentration below 12 µg/l is diagnostic for iron deficiency. In children, a cut-off value of 10 ug/l has also been suggested. Although a low serum ferritin level defines the onset of iron deficiency, it does not indicate the severity of the iron deficiency due to higher assay variability. Additional measurements such as transferrin saturation or transferrin receptor may be done (21).

As ferritin is an acute phase reactant, its serum levels may be elevated in the presence of chronic inflammation, infection, malignancy and liver disease. Correct interpretation of serum ferritin relies on using the appropriate reference range specific for age and sex. Serum ferritin can be easily measured using immunoradiometric assay (IRMA), radioimmunoassay (RIA) immunosorbent assays (ELISA). (22)

(b) Body iron stores

Body iron stores provide information on both the iron deficient and iron replete sectors of the population and are estimated by integrating several laboratory indices. Body iron is expressed in relation to the storage compartment. A positive value represents the amount of iron that can be removed without inducing a deficit in the functional compartment. A negative value denotes iron deficiency and represents the amount of iron that must be returned to the body before iron stores can accumulate. Iron stores of less than - 300 mg is similar to iron deficiency anaemia (abnormal haemoglobin and at least two other abnormal iron parameters). Iron replete subjects, iron stores are estimated quantitatively from the serum ferritin level. In individuals with iron deficiency anaemia, the deficit in circulating haemoglobin is used to measure the degree of functional iron deficiency. The main advantage of estimating body iron stores is that it defines iron status in the entire population (23).

(c) Serum transferrin levels

Transferrin saturation below 15% and red cell protoporphyrin above 100 mug/100 ml packed red blood cells shows iron deficiency anaemia (21).

(d) Haematrocrit

A haematrocrit value less than 33 % is suggestive of iron deficiency anaemia.

(e) Mean corpuscular haemoglobin concentration (MCHC)

A value less than 32 g/dl shows reduced iron status and the subject is suffering from iron deficiency anaemia.

To identify iron deficiency in children, age-specific reference ranges must be employed. A serum ferritin level of less than 10 or 12 µg/l is indicative of iron deficiency in children and is often used as a sole measure of iron status (23).

Infants Intellectual and Motor Performance

There is increasingly convincing evidence to suggest that iron deficiency impairs psychomotor development and congnitive function. As per Nancey Bayley Scale of development measures, motor and mental development and Dennr development screening test

(24) Studies have reported lower performance scores among infants who had been anemic for at last three months compared to those anemic for less than three months. No significant deficit was detected in infants with intermediate levels of iron deficiency or pre-anemic iron deficiency. Significant differences in mental development and motor development scores have been observed at haemoglobin concentrations less than 10.5 g/dl (mildly anemic) (25). The more severe and longer the anaemia, the greater the effect on developmental delays in infancy (Table 2). Children who are deficient in iron during infancy, even though they have been provided treatment for the condition at that time, after 10 years, are found to score significantly lower than controls on measures of mental and motor functioning (26).

Iron and Neurotransmitters

Iron is important to the normal development and functioning of dopamineric neurons and that early changes could lead to permanent damage.

Several mechanisms linking anaemia to altered cognition are possible. The most direct one are the changes that occur in structure and function of CNS (27). A significant decrease in non heme iron both in liver and brain without changes in hematocrit are observed and they clearly suggest appreciable decrease in content of iron in certain tissue. The significant effects on neurotransmitter receptors during early stages of iron deficiency indicate the deficits in both excitatory and inhibitory pathways of central nervous system (28). The neurotransmitter receptors remain in dynamic equilibrium and their regulation depends on the synthesis, metabolism and various other components in signal transduction cascade. The changes in neurotransmitter receptors may be due to their up and down regulation. There may be changes in affinity of ligand with receptor without affecting the number of receptors although the mechanism involved is not very clear. The increase in GABA but decrease in glutamate receptors can explain the effects on higher mental functions. Both GABA and glutamate pathway have been implicated in several other nervous system disorders. Thus it may be suggested that impairment of higher mental functions may be linked to changes in neurotransmitter receptors and consequent signal transduction processes in central nervous system. Clinical trials on animals have shown that latent iron deficiency produces significant alterations in metabolism of 5-hydroxytryptamine and brain iron content. That could not be recovered after iron rehabilitation(29). Effect of iron deficiency on intracellular messengers like calcium, cAMP / cGMP and protein kinases which regulate cellular responses is also been studied. Studies done on animals also indicate that with iron deficiency anaemia there is significant decrease in myocardial noradrenaline levels associated with increase in size of cardiac muscle cells. There are two ways in which iron deficiency could effect work performance and exercise capacity. Firstly, a reduced amounts of oxygen transported around the body. This is mainly used in brief, intense exercise. Secondly, iron deficiency may decrease the capacity of the muscle to consume oxygen. Muscular work lasting more then a few minutes requires the oxidative production of energy in the form a muscle mitochondria. This process requires the iron containing electron - transport proteins, cytochromes and iron-sulphur proteins. After iron supplementation, mean heart rate and energy expenditure at work are reduced and production efficiency is increased (30). Energy

Table 2. Developmental scales and cognitive tests used in studies on Iron deficiency anemia

Age	Measurements	Results
6-30 mo	Bayley Scales of Mental and Motor Development	Infant development scale constructed locally for purposes of study on Anaemic Children were found to be significantly reduced
36-84 mo	Peabody Picture Vocabulary Test	Battery of 10 to 22 tests of specific congnitive functions administered yearly beginning at 36 - 84 mo. For data reduction the respective scores were factor analyzed. A general and a memory factor emerged and was used for statistical analysis,reduced in anaemics
School age	Arithmetic test developed from school curriculum Peabody Picture Vocabulary Test	Psychoeducational test battery including tests of literacy, reading comprehension, numeracy, general knowledge, and Raven Progressive Matrices found to be reduced in Anaemic Children

can be conserved and cardiovascular stress and exertion reduced as iron status improved. Statistically non-significant trend for the association of low serum ferritin and depression has been noticed. A possible biochemical explanation may be attributed to the fact that rate limiting enzymes in the synthesis of catecholamines and serotonin are iron dependent (31). Serum ferritin predicts iron deficiency anaemia. A number of tests like mean cell volume, tranferrin saturation, red cell protoporphyrin, red cell volume distribution and red cell ferritin has been done. Serum ferritin was streets ahead in terms of diagnostic accuracy.

Iron deficiency anaemia results in tissue iron deficiency as well as reduction in circulating hemoglobin and causes the most severe functional liabilities. Iron deficient erythopoiesis can effect work capacity and exercise tolerance in adolescents. Neurological impairment in adult has been suggested to be another clinical consequence of iron deficiency but its extent is unknown (32). More sensitive psychometric tests and iron status parameters are required. The serum transferrin receptor may be a more sensitive iron status index for use in this area. No clinical consequence has been found as a result of low iron stores (24, 33).

Therapy

Treatment trials in children under two years of age : Short-term treatment trials

The first treatment trials were short, usually lasting less than two months, and produced no convincing evidence of benefit to children's developmental levels. Children who received short-term treatment showed improvements in scores on the Bayley Test of Mental Development (23), although there were no placebo anaemic groups, so that test practice could have accounted for the improvement. There is no convincing evidence that iron treatment of young children with iron deficiency anaemia has an effect on psychomotor development. Out of the two studies which treated children for two months or longer , one reported a dramatic benefit in developmental scores while other did not. This shows no clear evidence about the effect of therapy with oral or inject able iron in young children (34).

In adults

The treatment of iron deficiency with simple inorganic iron preparations such as ferrous sulfate tablets is usually highly effective. Failure to respond to oral ferrous sulfate is usually not due to malabsorption, but to the failure of the patient to take iron or due to gastro intestinal side effects, which can be minimized by administration with meals and reduction of dosage. The therapy should be continued for at least four months after the anaemia has been corrected in order to attain normal storage reserves(9,31).

CONCLUSION

Iron deficiency identifies children at concurrent and future risk of poor development. It is also concluded that iron deficiency is usually associated with many psychosocial, economic and biomedical dis-advantages. Studies has indicated that anemic children of less than 2 years have failed to catch up with non anemic children even after iron supplementation (35). Anemic children of more than 2 years also usually had poorer cognition and school achievements as compared to non-anemic once. They usually catch up in cognition with repeated testing and treatment but not in school achievement (33).

The iron deficiency during developmental stages of brain (i.e. fetus) may also cause irreversible disturbances and damages to GABA neurotransmitter system. Most of the co-relational and experimental studies done earlier confirmed the hypothesis that iron deficiency of mild to moderate nature has an adverse effect on congnitive development (3, 7). Therefore, it may be logical to suggest that impairment of higher mental function like cognition and learning in humans (5, 13) may be linked to changes in neurotransmitter receptors and consequent signal transduction process in the nervous system (28,29).

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